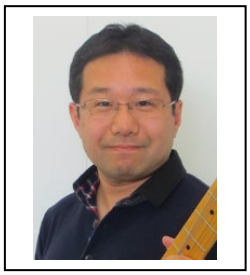


Biofunctional Synthetic Chemistry Laboratory
Chief Scientist: Katsunori Tanaka (Ph.D.)

(0) Research field
CPR Subcommittee: Chemistry, Biology

Keywords:
Molecular imaging, diagnosis/therapy, biofunctional molecules, glycan, therapeutic in vivo synthetic chemistry

(1) Long-term goal of laboratory and research background
Although many efficient bond-forming reactions have been developed in the field of synthetic organic chemistry, their utility typically fails to translate in complex mixtures present in cellular or living biosystems. As such, only a handful of effective labeling or conjugation methods in biosystems are readily available. To address this issue, we are synthetically exploring the unique reactivity of conjugated imines for their potential in novel chemical reactions. The benefit of this approach is that since a large part of amine-containing biomacromolecules are biosynthesized through imine chemistry, imine-mediated chemical reactions will not face the same challenges that classical synthetic organic chemical reactions face within living systems. In parallel to this work, our studies have also shown that the unique reactivity of imines could be involved in pathways that regulate biologically important processes.

Besides usage in methods of labeling or conjugation, the novel reactivity of imines, in combination with other advanced metal-catalyzed transformations, could alternatively be used in the multi-step synthesis of biofunctional molecules within living biosystems. Through a concept we refer to as “Therapeutic In Vivo Synthetic Chemistry”, we aim to develop an adaptable system where a cascade of organic transformations can be directly executed at target regions within the body during predefined times to generate a bioactive molecule that elicits a localized biological effect. Towards this goal, we are analyzing, with the use of molecular imaging, the complex “pattern recognition” mechanisms of natural glycans in vivo and applying the glycan-based interactions to direct various linked biomolecules to desired organs and tissues.

(2) Current research activities (FY2021) and plan (until Mar. 2025)
1. Localized therapy by in vivo metal-catalyzed reaction

We achieved the selective recognition of the target cells, even in vivo, by applying the “pattern recognition mechanism” of the glycoclusters. We used the glycoclusters as delivery system to carry the transition metal catalysts to cancer regions, in order to perform the desired organic transformation towards anticancer molecules (Fig. 1). We would synthesize various drugs and biologically active natural products to generalize our concept, “Therapeutic In Vivo Synthetic Chemistry”.

2. Chemical transformation of toxic substance to diagnostic molecule

We succeeded in transforming the acrolein, which can be selectively and with significant amounts produced in the cancer, to the diagnostic molecules in vivo. Thus we performed the sequential reactions in the cancer specimens, which were taken during the breast cancer surgery, to diagnosize various kinds of cancer within 5 minutes and with very simplified operation (Fig. 2). The method, named “Click-To-Release” has already successfully used in the clinical studies, and could be used soon in the hospitals worldwide. We would use such endogenous acrolein to synthetically convert to the therapeutic molecules to treat the cancer in vivo.

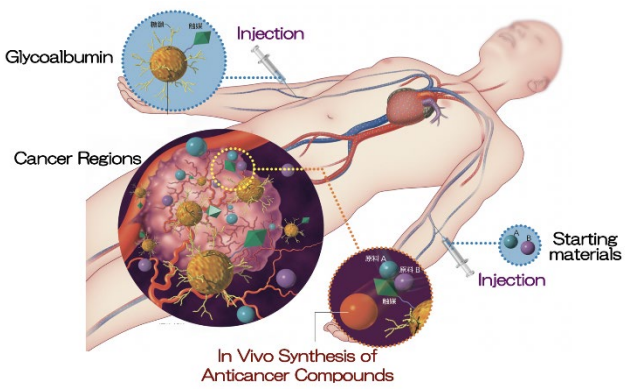


Fig. 1 Localized cancer therapy by in vivo metal-catalysis.

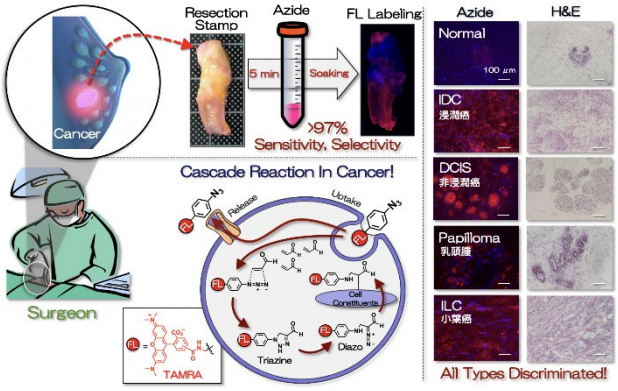


Fig. 2 Intraoperative diagnosis by cascade reaction in human cancer.

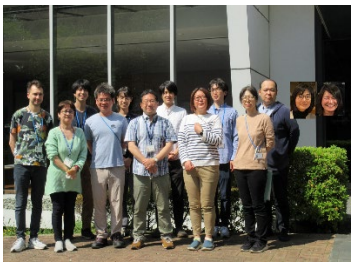
(3) Members as of March, 2022

(Chief Scientist)
Katsunori Tanaka
(Senior Research Scientist)
Akihiro Ishiwata
(Special Postdoctoral Researcher)
Tomoya Yamamoto
(Postdoctoral Researcher)
Tsung-che Chang, Igor Nasibullin, Ahmadi Peni, Akari Mukaimine
(Technical Staff)
Sayaka Urano, Akiko Nakamura
(Visiting Scientist)
Yukishige Ito, Kyohei Muguruma, Takefumi Murase, Yu Nakagawa, Ambara Pradipta, Satoru Tamura, Koji Morimoto
(Student Trainee)
Michitaka Kurimoto, Yudai Ode, Hiroyuki Michiba, Kazuki Terashima, Kyosuke Imai, Kenshiro Yamada, Takatsugu Kasahara, Natsuho Moritsuka
(Research Part-time Worker)
Yukiko Kusakari
(Assistant)
Masayo Ohara

(4) Representative research achievements

1. "Prodrug activation by gold artificial metalloenzyme-catalyzed synthesis of phenanthridinium derivatives via hydroamination", T.-C. Chang, K. Vong, T. Yamamoto, K. Tanaka, **Angew. Chem. Int. Ed.**, 60, 2-11 (2021).
2. "Targeted 1,3-dipolar cycloaddition with acrolein for cancer prodrug activation", A. R. Pradipta, P. Ahmadi, K. Terashima, K. Muguruma, M. Fujii, T. Ichino, S. Maeda, K. Tanaka, **Chem. Sci.**, 12, 5438-5449 (2021).
3. "Disrupting tumor onset and growth via selective cell tagging (SeCT) therapy", K. Vong, T. Tahara, S. Urano, I. Nasibullin, K. Tsubokura, Y. Nakao, A. Kurbangalieva, H. Onoe, Y. Watanabe, K. Tanaka, **Sci. Adv.**, 7, eabg4038 (2021).
4. "Epoc group: Transformable protecting group with gold(III)-catalyzed fluorene formation", T. Yamamoto, T.-C. Chang, K. Tanaka, **Chem. Sci.**, 12, 10703-10709 (2021).
5. "In vivo metal-catalyzed SeCT therapy by a proapoptotic peptide", P. Ahmadi, K. Muguruma, T.-C. Chang, S. Tamura, K. Tsubokura, Y. Egawa, T. Suzuki, N. Dohmae, Y. Nakao, K. Tanaka, **Chem. Sci.**, 12, 12266-12273 (2021).

Supplementary
Dr. Tanaka holds concurrent roles as a Chief Scientist at the RIKEN and as a Professor at the Tokyo Institute of Technology.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